[NATI]ONAL CANCER INSTITUTE

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VIRUS-CANCER RESEARCH

U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
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NATIONAL CANCER INSTITUTE • RESEARCH REPORT NO. 2

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PREFACE

The effort to identify the causes of cancer has a high priority in biomedical research today. The causes of human cancer are not entirely unknown, for chemicals and radiation have been proved to cause some types and are strongly suspected of being involved in many others.

Time and time again, especially during the period around the turn of the century, all sorts of bacteria, fungi, and the like were said to cause cancer, largely, often solely, on the strength of their presence in tumors. None of these theories was long lived, however, for it is one thing to find bacteria in tumors and quite another to demonstrate that they caused the tumors.

As a result, there was a period in which some researchers frowned on suggestions that viruses might play a role. The science of virology has come a long way since those days. Thanks to the introduction of tissue culture, electron microscopy, and many other sophisticated techniques, researchers can now hope eventually to come up with an answer to the question of whether viruses cause human cancer. Evidence that they do may pave the way for the development of new preventive measures and may even open new vistas in the treatment of cancer.

As the principal Federal agency conducting and supporting cancer research, the National Cancer Institute is spearheading a broad attack on the virus-cancer problem as one part of its total program of research on the causes, detection and diagnosis, and treatment of cancer.

At the headquarters of the National Institutes of Health in Bethesda, Md., a few miles outside Washington, D.C., members of the National Cancer Institute's scientific staff are conducting extensive studies on the relationship of viruses to cancer. Across the country and around the world, scientists in scores of other

institutions are engaged in similar work. Their research, in many instances, is supported in part by grants from the National Cancer Institute. A recent tabulation showed that the current annual value of grants for virus-cancer research is approximately $7,300,000.

The National Cancer Institute also administers a nationwide program in which urgently needed virus-cancer research materials are being developed and made available to investigators. The current annual level of contracts for this program is approximately $3,400,000.

And finally, the National Cancer Institute has organized a Human Cancer Virus Task Force composed of some of its own staff scientists, as well as prominent investigators from other institutions, to plan and carry on an intensive research effort focused on the role of viruses in causing human cancer.

This report describes and explains some of the approaches currently being utilized in virus-cancer work. Future publications in this series will deal with studies of many other aspects of cancer research.

VIRUSES: what they are what they do

Viruses lie at the threshold of life. They are parasites that cannot multiply in any environment except living tissue. They are capable of doing damage out of all proportion to their submicroscopic size.

That they are indeed on the borderline between the living and the nonliving was proved by Dr. Wendell Stanley, who won a Nobel Prize for his classical experiment with a virus that causes the so-called mosaic disease in tobacco plants. The tobacco mosaic virus particles were isolated as crystals, which seemed to have no more life in them than there is in a lump of coal, but when these same crystals were rubbed into the leaves of a tobacco plant, the virus sprang to life again.

Too small to be seen through ordinary microscopes, most virus particles are visible only with the aid of powerful electron microscopes that magnify them 100,000 times or more. Though many are spherical, or roughly so, some, such as the tobacco mosaic virus, are rod shaped, while others, including some of the viruses that infect bacteria, are tadpole shaped.

Though smaller by far, and less complex, than any of the millions of cells in the human body, or, for that matter, in a plant or an animal, viruses have one essential thing in common with those cells. It is that the nucleus of every living cell and the core of every virus particle contain nucleic acid.

The type found in cell nuclei is primarily DNA—chemical shorthand for deoxyribonucleic acid—the substance of which chromosomes are made. DNA is the bearer of hereditary information; the blueprints for new cells, as well as new men, are embodied in the four-unit chemical code of DNA. As nature's storehouse of information, DNA is a prototype of the complex electronic machinery man uses for the same purpose, and indeed, for efficiency in data storage and retrieval, it surpasses the best man has been able to do so far. The DNA in cells also serves as

a template for the production of another type of nucleic acid, known as RNA (ribonucleic acid), which in turn governs the structure of proteins, the building blocks of life.

The nucleic acid in viruses is either DNA or RNA, and viruses are often referred to by the type they contain. Thus, vaccinia virus (used for smallpox vaccination) is spoken of as a DNA virus, and the polio viruses are RNA viruses. The nucleic acid forms the core of a virus particle and is wrapped in a coat made of protein.

In an experiment performed several years ago with tobacco mosaic virus, Dr. Heinz Fraenkel-Conrat of the University of California demonstrated one of the roles of the viral nucleic acid. For this experiment, the protein coats were stripped from two slightly different types of the virus and mixed with the nucleic acid from the other type. The virus particles formed in each mixture appeared to be similar, on the basis of laboratory tests, to the type that had donated the protein, but when they were used to infect tobacco plants, the disease that resulted and the new virus particles formed in the infected plants corresponded to those typical of the donor of the nucleic acid. Thus, the viral nucleic acid was shown to transmit hereditary traits from one generation of viruses to another, as it does in cells.

The viral nucleic acid plays another role, for by itself it will produce the same disease as a complete virus particle. This has been demonstrated with nucleic acid from many common viruses, including that of tobacco mosaic, polio, and influenza viruses. The only difference appears to be a reduction in potency, which is understandable when the nucleic acid is deprived of the protection of a protein coat, which guards it against destruction by enzymes.

In spite of the many advances made in recent years in knowledge of what viruses are and what they do, the task of figuring out how they cause disease is a tough one, for viruses do their damage inside cells. One result is that man's understanding of the processes by which they produce their effects is limited largely to the little that can be learned from studying the symptoms of virus-caused diseases.

As if to help researchers with this problem, Nature designed

some viruses to infect bacteria, thus matching one kind of parasite against another in a conflict that can be monitored in the laboratory. It is known that the tadpole shaped bacterial viruses attach their tails to bacterial cells, bore a hole in the cell membrane, and inject their nucleic acid. Once inside the cell, the viral nucleic acid diverts the cellular resources from their usual functions to the manufacture of new virus particles. Eventually, those resources are exhausted. The cells, by then filled to the bursting point with virus particles, rupture, and the newly formed particles are released to begin stalking new victims.

Essentially the same process goes on in many of the common human virus infections, such as polio, the basis of which is the destruction of cells. The big difference is that man has means of protecting himself; namely, by forming antibodies that kill the virus or "disarm" it.

Evidently, some viruses, instead of killing cells, may do just the opposite: cause them to proliferate. Also, some viruses that kill cells under some circumstances may cause proliferation under others. This could explain why viruses might cause cancer.

VIRUSES: the jump from animals to man

Do viruses cause human cancer?

The only answer that can be given at present is that they are responsible for such a variety of cancers in animals that it would be surprising if they did not cause some types in man, for the basic phenomena of life do not differ very much from one species to another.

This does not imply that viruses are suspected of causing all cancers. On the contrary, cancer is assumed to be a group of diseases, rather than one, and to have many causes, some of which are already known. Excessive doses of ionizing radiation, for example, are known to have caused some cases of leukemia and bone cancer. Also, the unusual frequency of specific forms of cancer among workers in certain industries has often been traced to chemicals with which they worked.

There is, of course, much to be learned about radiation and chemicals as causes of human cancer, and research aimed at clarifying their roles is continuing. At the same time, the suspicion that viruses also play an important role is being pursued more vigorously than ever before.

Evidence linking viruses and cancer began accumulating early in the 1900's with a report that leukemia in chickens had been found to be virus caused. Then, in 1911, Dr. Peyton Rous at the Rockefeller Institute laid the cornerstone of modern virus-cancer research by demonstrating that a virus that now bears his name causes sarcomas in chickens. At that time, however, and for many years afterward, the idea that viruses might cause human tumors was given little serious consideration.

During the 1930's, viruses were found to cause tumors in other species, including papillomas in rabbits and mammary tumors in mice. Then, a decade ago, viruses were linked to several types of leukemia in mice, and, in experiments that did much to revive interest in virus-cancer work, a single virus was shown to produce

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some 20 different types of tumors in mice. These were the events that led to today's intensive efforts to find out whether viruses cause human cancer.

To prove that a disease is virus caused requires, as a minimum, isolation of the virus from individuals who have the disease and evidence that it induces the same or a very similar disease in other individuals, preferably of the same species as the diseased individuals. To find out, for example, whether a mouse tumor is virus caused, the usual approach is to prepare a cell-free extract of the tumor tissue and inoculate it into other mice in an attempt to produce tumors identical to the original one.

One of the troubles with this approach is that tumor viruses cannot always be isolated from the tumors they cause, as researchers know from their experience with animal tumor viruses. A low dose of Rous sarcoma virus, for example, may produce tumors in chickens from which little or no virus can be recovered, as demonstrated by Dr. W. Ray Bryan at the National Cancer Institute. An interesting explanation of this phenomenon has come from studies by Dr. Harry Rubin at the University of California, which indicated that the Rous virus is "defective." Though it induces tumors, new virus particles evidently are not formed in the absence of a second, or "helper," virus.

One way of coaxing tumor viruses out of hiding is to place them in an environment free of at least some of the biological forces that might inhibit them in an intact animal. Tissue culture—the technique of keeping cells alive in the laboratory—offers such an environment. Tissue culture was instrumental in the development of polio vaccines, because it permitted the propagation of polio viruses in the quantities required for vaccine production.

Its role in tumor-virus work is exemplified by experiments in which a virus found in leukemias and salivary-gland tumors in mice was found to produce more than 20 types of mouse tumors after being propagated in tissue culture. To symbolize the wide range of tumors this virus produces, it is referred to as "polyoma virus," and it has been shown to produce tumors also in rats and hamsters. The experiments that revealed its full potential were performed at the National Institutes of Health by Drs. Sarah E. Stewart and Bernice E. Eddy.

A potential detour around the problem of recovering viruses lies in the knowledge that the nucleic acid of a virus will produce essentially the same effect as the complete virus, and it is possible that tumors that appear virus free may contain "incomplete" virus, or in other words, only the viral nucleic acid. This is consistent with the modern concept of viruses as "bits of heredity in search of a chromosome," which, spelled out in terms of tumor viruses, would suggest that the viral nucleic acid enters a cell and occupies a place on a chromosome. Thus, it would become, in effect, a new or extra gene that would endow the cell with a new hereditary trait—the potential for becoming malignant.

Tumor-inducing nucleic acid has already been extracted from rabbit papillomas that appeared to contain no virus when tested by conventional methods and from polyoma-virus-infected cells in tissue culture. As techniques for isolating nucleic acids are refined and improved, this approach is bound to be more widely employed.

The necessity of substituting animals for man in testing potential tumor viruses or tumor-inducing nucleic acids raises additional problems. To begin with, most viruses have a limited range of infectivity, or in other words, they will attack only a few types of cells and tissues and only certain species and certain strains of inbred laboratory animals. The polio viruses, for example, specifically invade and destroy nerve cells and infect only man and some types of monkeys.

Animal tumor viruses originally appeared to be more restricted in this respect than are most other types, but many exceptions have since been found. Nonetheless, monkeys and other subhuman primates are being used increasingly in virus-cancer research in the hope that, because of their close evolutionary relationship to man, they will prove susceptible to human cancer viruses.

A number of other points that have been established in work with animal tumor viruses also have a bearing on the approaches utilized in the search for human cancer viruses. One is that the occurrence of virus-caused tumors in animals depends not only on the type and dose of virus to which the animals are exposed, but also on many characteristics of the animals them-

selves. Their age at the time of exposure is especially important. The use of newborns, for instance, rather than mature animals, was the key to the success of experiments in which Dr. Ludwik Gross at a Veterans' Administration Hospital in New York demonstrated the role of a virus in the high incidence of leukemia in an inbred strain of mice.

Animals' sex, genetic heritage, and hormonal condition also influence their response to tumor viruses. The occurrence of most mammary tumors in mice, for example, depends on a virus, the animals' inherited susceptibility to the virus, and hormonal stimulation of the mammary glands. For lack of the proper "soil," the mammary tumor virus, which is commonly transmitted from mother to offspring in the milk, may pass repeatedly from one generation to another without producing tumors. That a virus was involved was first demonstrated by the late Dr. John J. Bittner at Jackson Memorial Laboratories in Maine.

Even when conditions are favorable, there is always a lag, or latent period, between exposure of an animal to a tumor virus and the appearance of a tumor. The latent period may range from a few days, which is rare, but true, for instance, of the Rous sarcoma virus in chickens, to several months, and in the case of the mammary tumor virus, almost a year, or half the lifetime of a mouse.

A long latent period increases the difficulty of establishing the origin of tumors that occur in animals inoculated with human tumor extracts. This is especially troublesome in species such as mice and rats, for in the usual laboratory types the incidence of spontaneous tumors increases with advancing age. Also, the animals are likely to be harboring many viruses of their own, including latent tumor viruses, any of which might be triggered by experimental procedures.

Again, the use of monkeys and similar primates, especially those born and reared in germ-free environments, may be the answer, but perhaps at the cost of latent periods of many years. Another promising approach is the use of smaller, shorter lived animals, especially mice, whose virus population is defined; that is, known to the researchers using them. Only limited numbers

of such animals are now available, and efforts to increase the supply are being made.

Thus, the techniques of virus-cancer research have begun to catch up with the problems. This enables researchers to focus their efforts profitably on specific types of cancer for which the evidence of viral origin is especially suggestive. At the moment, many scientists are concentrating on the leukemias, especially acute leukemia, and to some extent on the closely related lymphomas.

VIRUSES: in leukemias and lymphomas

As a close-in suburb of Chicago, Niles, Ill., is probably known to few people outside the sprawling metropolis of which it is part. To many people who do know of it, Niles is the place where eight cases of leukemia occurred in children between the fall of 1957 and the summer of 1960. Seven of the eight children attended the same parochial school, and the eighth had friends among pupils at the parochial school. For a community of 20,000, the 8 cases within 3 years represented 4 times the number that would have been expected on the basis of the nationwide incidence of leukemia. The facts suggest, but do not prove, that the disease was of infectious origin.

On the opposite side of the world, in a belt extending across central Africa, there has been an unusually high incidence of a type of lymphoma involving the jaw. There, too, children are the victims. The geographical pattern of the cases together with the topography and climate of the area suggest that the disease may be caused by a mosquito-borne virus, though there are as yet no biological data to support that theory. To date, the search for such a virus has been fruitless.

The bulk of the evidence that has led many researchers to focus their efforts on the leukemias has come from studies of these diseases in animals. Leukemia in chickens was, in fact, the first type of cancer ever shown to be virus caused. Leukemias and lymphomas occur so commonly in domestic fowl that they create an economic problem in the poultry industry. There is some similarity between the leukemia-lymphoma complex in fowl and the same spectrum of diseases in man, which lends significance to the question of whether there are just a few fowl leukosis viruses, each of which can produce a wide range of disorders, or a large number whose individual range of effects is limited.

Over the last decade, research on leukemia in mice has been especially productive. Following the first isolation of a mouse

leukemia virus, so many have been found that, in the words of one scientist, "Some investigators accept, and none can vigorously refute, the generalization that leukemia in mice is a virus disease."

The various mouse leukemia viruses produce diseases that differ in many respects. One of the latest to be found was isolated at the National Cancer Institute by Dr. Frank J. Rauscher and is unusual in that it acts very rapidly to produce massive enlargement of the spleen, leading to death in some mice and leukemia in those that survive this initial effect.

One of the most intensively studied of the mouse leukemia viruses was isolated also at the National Cancer Institute by Dr. John B. Moloney. Originally isolated from a transplanted mouse tumor in which it had evidently been a "passenger," the virus induces leukemia in both mice and rats. Not long ago, in studies with the electron microscope, Dr. Albert J. Dalton found typical virus particles "floating" in the blood of animals in which leukemia had been induced by inoculation of this virus.

That finding indicated that the virus might be recovered from the blood without the debris (parts of cells and other matter) that is inevitably picked up when the spleen, lymph nodes, and other solid tissues are used as the source of virus. The researchers found that by spinning the blood in a centrifuge 4 times at increasingly high speed up to 30,000 times the force of gravity, they could obtain a tiny pellet containing essentially pure virus.

Then, when extremely thin slices of such pellets were examined through an electron microscope, the virus particles appeared to have tails. They seemed, in other words, to have a tadpole-like shape similar to that of many of the viruses that infect bacteria. Additional study supported the impression that the particles did indeed have a six-sided head and a well-formed tail, which is now assumed to represent the mature form of the virus, as opposed to the previously seen spherical particles, which evidently are an earlier stage in the development of the virus.

These findings have prompted many investigators to begin searching for viruses in the blood of acute leukemia patients. At the National Cancer Institute and other institutions across the country, electron microscopes are being utilized to screen blood specimens for particles that might conceivably represent human

leukemia viruses. As no one knows exactly what shape such particles might have, it is being assumed, at least for the time being, that they would look something like their counterparts in mice and rats.

The specimens that appear to contain particles that might represent viruses are being tested in animals, especially monkeys, and in tissue culture in the hope that, like the polyoma virus, any leukemia viruses present in the specimens will "show their colors" after a period of cultivation in the laboratory.

VIRUSES: in search of disease

Over the last several years, it has become popular to blame viruses for all sorts of illnesses. Forced to remain at home for a day or two by some minor disorder, most people refer to their trouble as "just a virus."

More often than not, they are probably right. In the wake of advances in the techniques of virology, the number of known human viruses has multiplied at an incredible rate. Their number has grown so rapidly that researchers do not know what diseases, if any, many of them cause.

There is, in fact, a group known as orphan viruses, not known to cause any particular disorders. As a result, they have come under suspicion as possible cancer viruses, though conclusive evidence one way or the other is lacking. Now, the possible roles of two other groups of viruses are being studied. One includes some known primarily as causes of noncancerous diseases, such as adenoviruses, and the other comprises certain animal viruses to which man has been inadvertently exposed. The best known example of the latter type is SV40, a monkey virus that contaminated some early lots of polio vaccines.

Every man, woman, and child probably plays host to many different viruses with only occasional ill effect. Among the most widespread of all are the adenoviruses, some of which are known to cause respiratory diseases similar to the common cold and influenza. More than 2 dozen separate adenoviruses have been identified. Two of them, adenoviruses Nos. 12 and 18, have been shown to produce tumors in hamsters.

This does not necessarily mean that they cause human cancer. To understand why not, take the case of polyoma virus. As explained previously, polyoma virus propagated in tissue culture is an extremely potent tumor-inducing agent in young animals. And yet, polyoma is found in wild mice in fields and cities, but in those environments it seldom, if ever, causes any tumors.

On the other hand, some animal viruses do cause tumors in their natural hosts. The mouse mammary tumor virus is one. The avian leukosis viruses, which cause leukemias, lymphomas, and sarcomas in chickens, are another example. The problem, therefore, is to determine which of these categories the adenoviruses fit into. Are they a cause of cancer in their natural host, man, or only in laboratory animals?

One of the first things learned about adenovirus-induced tumors in hamsters was that the viruses cannot be recovered from the tumors. An old and familiar story in tumor-virus work, its implications for the human cancer problem are obvious: if adenoviruses play a role, some other way of tracking them down may be needed.

At the National Institute of Allergy and Infectious Diseases, Dr. Robert J. Huebner and his colleagues have found a promising method. They discovered that the adenoviruses, like careless criminals, leave a sort of "fingerprint" in the tumors they produce in hamsters.

Thus, even though the viruses themselves elude detection, antibodies to them are found. They are not the usual adenovirus antibodies, but a special type whose nature suggests that the tumor cells contain the viruses in an incomplete form. The no-two-alike rule seems to apply to adenovirus "fingerprints," at least to those for Nos. 12 and 18, which enhances their usefulness as means of identifying tumors caused by adenoviruses.

As for SV40, it, too, has been shown to cause tumors in hamsters. There is no evidence that it does so in its natural hosts—rhesus and cynomolgus monkeys. Yet to be answered, however, is the question of what, if anything, it does in man. A number of groups of researchers have shown that SV40 causes bizarre changes in human cells growing in tissue culture. That these changes make the cells malignant remains to be proved.

The answers to the questions now being asked about the cancer-producing potential of both SV40 and the adenoviruses may come from studies of man himself, for the adenoviruses are naturally widespread in the population, and SV40 has been given inadvertently to large numbers of individuals in polio vaccines.

A search for evidence of the presence of adenoviruses, or perhaps for their "fingerprints," in cancer patients is, therefore, a potentially fruitful, though costly, way of attacking the problem.

Some of the individuals who received SV40 in polio vaccines are under surveillance, but so far there is no evidence of an unusual incidence of cancer in the group.

VIRUSES: in our modern environment

The environment in which man lives and works today is far more complex than it was only a generation or two ago. As a result of industrial and technological progress, the number and variety of chemicals in the air and water and in food products have multiplied many times over, and levels of ionizing radiation have increased. There are, in addition, many natural elements, such as viruses.

Thus, man is exposed continuously and simultaneously to a broad spectrum of biological, chemical, and physical forces. To make matters even more complicated, every individual reacts somewhat differently to these forces. Everyone's reaction is conditioned by heredity, by his age and sex, and by a multitude of other factors.

If the evidence now in hand suggests one conclusion more strongly than any other, it is that there probably are multiple causes for every type of cancer. Take, as an example, the known role of radiation in causing leukemia. Among survivors of the atomic bomb detonations in Hiroshima and Nagasaki, the incidence of leukemia rose sharply. And yet, it reached a maximum of only one in 100 among those who received the highest doses of radiation. Of every 100 in that category, 99 have not developed leukemia (though it is too soon to say that they may not develop other types of cancer in the years to come).

The question, then, is not why the incidence was so high, but why it was not higher. Evidently, something besides excessive radiation is needed for leukemia to arise. The chances are that many other forms of cancer are the result of a combination of causes, including either radiation or chemicals, or both, plus other factors.

Viruses might well be one of the other factors. Among the likely candidates are the many viruses that individuals carry for long periods, in some instances for their entire lifetime, without

ill effect unless something happens that triggers their latent ability to cause cancer. The occurrence of cancer in animals as a result of the joint effects of viruses and other factors is a well known phenomenon.

The late Dr. Francisco Duran-Reynals pioneered in demonstrating that viruses that normally do not cause cancer would do so in animals also treated with cancer-causing chemicals in doses too small to produce tumors by themselves. Thus, vaccinia, or cowpox, virus was shown to produce tumors in mice at sites of inoculation that had been painted with a chemical.

Of greater significance, perhaps, to the environmental problem is the occurrence of lung cancer in mice exposed to both influenza virus and ozonized gasoline in experiments performed at the University of Southern California by Dr. Paul Kotin (now a member of the staff of the National Cancer Institute) and his colleagues. Neither the virus alone nor the gasoline fumes alone caused any tumors, but the mice exposed to both developed lung tumors similar to the type most common in man.

There is also evidence that radiation can trigger a latent cancer-causing virus. This came from experiments in which leukemia was induced in mice by exposing them to radiation and then reproduced in other mice by inoculating them with cell-free extracts of leukemic tissue from the irradiated animals.

The question that runs through all these experiments is akin to the old argument over the chicken and the egg. That is, did the chemicals and radiation cause some change that modified the animals' response to viruses that ordinarily would not have caused any tumors, or did the viruses lower the animals' threshold of susceptibility to the radiation and chemicals? Data to resolve the puzzle are lacking, but either way it seems certain that in these cases viruses played a role in the sequence of events leading to the development of tumors.

VIRUSES: prevention and therapy

Over the last several years, medical science has scored a number of encouraging gains in its efforts to free man of the burden of virus-caused diseases. The bulk of the progress has been in prevention, with the introduction of vaccines that have all but wiped out the threat of polio and the more recent development of a measles vaccine. As for treatment, much less has been accomplished, but the recent news of a drug effective against a virus-caused eye disease has aroused hopes for additional advances in the near future.

Everyone is, of course, endowed with natural defenses against disease-causing viruses, bacteria, and the like. The chances are that before the introduction of polio vaccines, for example, polio viruses were far more widespread in the population than might be expected from statistics on the occurrence of the disease. Thousands of individuals, perhaps, were infected who never had any sign of polio, thanks to the body's natural defense mechanisms.

The body has two types of defenses: the nonspecific, of which the skin is an example in its role of keeping foreign matter from entering the body, and the specific, the backbone of which are substances appropriately known as antibodies. So specific are they that antibodies to smallpox virus, for instance, offer no protection against polio viruses.

Though the intricacies of antibody production are not fully understood, it is known that antibodies are formed in response to invasion of the body by foreign substances, or antigens, which may be anything alien to the human body, from viruses to ragweed pollen.

The body's ability to resist such invaders is known as immunity, which is not, by any means, an all-or-none condition. It varies in both degree and duration, depending not only on the individual but also on the antigen, some of which do not provoke very high levels of antibody production. Thus, one siege of the

measles confers an immunity that usually keeps a person from coming down with the disease again, but, as everyone knows, one common cold is almost always followed by others. The same thing is true of vaccination, which is why physicians recommend periodic revaccination against smallpox.

Vaccines are, in essence, antigens and contain the very same viruses they are designed to combat. They stimulate production of antibodies, but the viruses in them have been specially treated to knock out or weaken their ability to cause disease.

That vaccines will protect animals against certain tumor-causing viruses has already been demonstrated. An experimental vaccine has been prepared that protects mice against one of the mouse leukemia viruses, and another has been developed that increases the frequency with which rabbit papillomas regress instead of becoming malignant.

However, it is a big jump from vaccines that work in animals to vaccines that are both safe and effective for human use, and to bridge the gap, much has to be learned about the immunological interplay between cancer-causing viruses and their hosts and about the routes by which such viruses are transmitted.

One of the big questions is whether the still-to-be-found human cancer viruses provoke any immune reaction in man. The answer will depend to a considerable extent on the degree to which such viruses differ antigenically from human tissue; that is, on how foreign they are. There is some evidence that among animal tumor viruses, the RNA types are less antigenic than the DNA types, or in simpler terms, do not induce as high a level of antibody production. The reason evidently lies in their different sites of replication. The RNA viruses appear to be formed in the cytoplasm of the cell and to contain some cellular protein in their coat, while the DNA viruses seem to replicate in the nucleus.

The means of transmission are important because the time of life at which a host is exposed to a tumor virus has been shown to influence its reaction. Experiments at the University of California showed that chickens did not form antibodies to a tumor virus with which they were born and that the incidence of disease in these congenitally infected birds was higher than

in birds infected by contact, though it is important to note that the actual numbers of tumors were small in both groups.

As already noted, the mouse mammary tumor virus is transmitted most effectively in mothers' milk, as is the mouse leukemia virus isolated by Dr. Moloney. Polyoma virus, as well as the chicken leukosis viruses, are spread by excreta and saliva. Other means of transmission have been demonstrated for various other tumor viruses. Though little or nothing is known of the ways in which the hypothetical human cancer viruses travel, there is no evidence, either from biological investigations or from studies of the pattern of cancer occurrence, that cancer in any form is a contagious disease.

Because so much remains unknown that has an important bearing on the problem, it is impossible to predict when vaccines might be available that would protect man against cancer or even to say with certainty that such vaccines will ever be developed. Working on the old Chinese adage that a thousand-mile journey begins with a single step, researchers are concentrating their energy on isolating human cancer viruses, for until that is accomplished, work on human vaccines cannot begin.

The prospects for early advances in drug treatment of virus diseases are equally difficult to forecast, but there are some hopeful signs. One is the recently acquired knowledge that a chemical known for short as IUDR, originally synthesized as a potential anticancer drug, offers effective treatment for a virus-caused eye disease, which, if unchecked, leads to blindness. The same chemical has been shown to interfere with vaccinia (cowpox) infection in animals and to inhibit the induction of tumors in hamsters by adenoviruses. If these findings are any harbinger, then the future of antiviral chemotherapy is indeed bright, though its value in the treatment of cancer remains uncertain.

COMMENT AND CONCLUSION

There are many promising approaches to solution of the cancer problem. In general, cancer research is divided into efforts to identify the causes of cancer, to devise improved means of detecting and diagnosing it, and to find increasingly effective methods of treatment. Within these broad groupings, and because the various forms of cancer are manifestations of abnormal growth, researchers follow their own interests and scientific judgment into studies of the most intimate details of life down to the level of single cells. Thus, every approach that has a reasonable scientific basis is explored to the fullest possible extent.

This report has attempted to summarize one segment of cancer research—one avenue of inquiry into the causes of cancer. The work discussed in these pages offers evidence of two notable trends in the search for human cancer viruses. One is the ever increasing role in virus-cancer research of such disciplines as biochemistry, genetics, and immunology. The other is a move toward investigations of the roles of virus, chemicals, and radiation jointly rather than separately.

A consensus seems to be emerging in favor of the concept that cancer arises as a result of an alteration in the genetic material of cells, that is, in the DNA-containing chromosomes, which might be caused by any of a number of factors acting individually or in concert. Though this might seem, on first glance, to increase the difficulty of devising means of prevention, another, and perhaps more realistic, way of interpreting it is that with increasing understanding of the chain of events that leads to cancer, researchers will discover opportunities to break the chain equally effectively at any of several different points.

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